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APPELLANTS' BRIEF

In re Application of David V. Goeddel and Mike Rothe

Tumor Necrosis Factor Receptor-Associated Factors

Serial No. 08/779,599

Filed: January 7, 1998

Examier: J. Ulm

Group Art Unit: 1646

Atty Dkt No. P0897C2

TABLE OF CONTENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of

David V. Goeddel and Mike Rothe

Serial No.: 08/779,599

Filed: January 7, 1997

For: TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED FACTORS

Group Art Unit: 1646

Examiner: J. Ulm

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, BOX AF, Washington, D.C. 20231.

May 13, 1998

Aida A. Miclat

APPELLANTS' BRIEF

BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Appeal Brief, filed in triplicate in connection with the above-identified patent application, is in response to a final Office Action mailed December 30, 1997 (Paper No. 10) and to the Advisory Action mailed February 3, 1998 (Paper No. 13). A Notice of Appeal was filed on January 20, 1998. The present Appeal Brief is accompanied by a Request for a Two-Months Extension of Time. This filing is, therefore, timely.

The Commissioner is hereby authorized to charge the fee set forth in 37 C.F.R. §1.17(c), the extension fee, and any additional fees or credit any overpayment to Deposit Account No. 07/0630.

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I.

REAL PARTY IN INTEREST

Genentech, Inc. of South San Francisco, California is the owner by assignment of the above-identified patent application. The assignment document was recorded at the Patent and Trademark Office on August 8, 1994, under Reel: 7095, Frame: 0077.

II.

RELATED APPEALS AND INTERFERENCES

Appellant is not aware of any related appeals or interferences which will directly affect, be directly affected by or have a bearing on the Board's decision in the pending appeal.

III.

STATUS OF CLAIMS

The present application, which is a continuation of application Serial No. 08/250,858 filed on May 27, 1994, now U.S. Patent No. 5,708,142 issued on January 13, 1998, was filed with Claim 1. Claim 1 was canceled in a Preliminary Amendment filed on January 7, 1997, concurrently with the filing of the present application. The same Preliminary Amendment added Claims 31-33. Claims 31-33 were amended in Applicants' Amendment under 37 C.F.R. §1.111 dated October 8, 1997, and the amended claims were finally rejected in an Office Action dated December 30, 1997. As no further claim amendments were proposed, the claims on appeal are once-amended Claims 31-33, which are reproduced in Appendix A attached herewith.

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IV.

STATUS OF AMENDMENTS

No amendments to the claims have been made subsequent to their final rejection.

V.

SUMMARY OF INVENTION

The present invention concerns an isolated novel human protein, human tumor necrosis factor receptor associated factor (designated as human "TRAF"), which is characterized in finally rejected claims 31 to 33 by its process of preparation.

Claim 31 specifies that human TRAF is prepared by first identifying a DNA molecule encoding human TRAF by screening a human recombinant cDNA library with oligonucleotide probe(s) having about 30 to 50 bases, derived from nucleotide sequences encoding murine homologues (designated "TRAF1" and "TRAF2", respectively) of the human TRAF protein, under stringent hybridization conditions which are specifically recited in the claim [Step (a)]; and producing the human TRAF protein encoded by a DNA molecule identified by cross-species hybridization, by conventional steps of recombinant DNA technology [Steps (b) - (e)].

Claim 32 specifies that the hybridization probe is derived from murine TRAF1.

Claim 33 specifies that the hybridization probe is derived from murine TRAF2.

The nucleotide sequence of murine TRAF1 is shown in Figure 10, SEQ ID NO: 1; the nucleotide sequence of murine TRAF2 is shown in Figure 11, SEQ ID NO: 3. The nucleotide and the deduced amino acid sequences of human TRAF protein are not disclosed in the present application.

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VI.

ISSUES

In the final Office Action mailed on December 30, 1997 (Paper No. 10), the Examiner rejected claims 31 to 33 under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which is not described in the instant specification in such as way as to (a) reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, or (b) to enable one skilled in the art to make and use the claimed invention.

Claims 31 to 33 were further rejected under 35 U.S.C. §112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the claims were rejected for their recitation of the term "about." The claims were further rejected under the same section on the ground that the specification allegedly fails to identify that material property or combination of properties which is unique to and, therefore, definitive of a TRAF protein.

These rejections were maintained in the Advisory Action mailed on February 3, 1998.

Accordingly, the issues presented on appeal are:

(A) Whether product-by-process Claims 31 to 33 reciting a process for the recombinant production of a human TRAF protein not identified by its amino acid sequence or any other material property, meet the written description and enablement requirements of 35 U.S.C. §112, first paragraph, if the process is disclosed in a manner that complies with 35 U.S.C. §112, first paragraph.

(B) Whether product-by-process Claims 31 to 33 reciting a process for the recombinant production of a human TRAF protein not identified by its amino acid sequence or any other

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material property, meet the requirements of 35 U.S.C. §112, second paragraph, if the claim recites material parameters of the process by which the protein is produced.

(C) Whether Claims 31 to 33 are made indefinite under 35 U.S.C. §112, second paragraph by their recitation of the term "about" in connection with the length of an oligonucleotide probe used for screening a human recombinant cDNA library.

VII.
GROUPING OF CLAIMS

For the purposes or this appeal, Claims 31-33 stand or fall together.

VIII.
ARGUMENT

A. THE FINAL REJECTION OF CLAIMS 31 TO 33 UNDER 35 U.S.C. §112, FIRST PARAGRAPH IS IMPROPER AND SHOULD BE WITHDRAWN.

Claims 31 to 33 stand finally rejected under 35 U.S.C. §112, first paragraph for alleged lack of adequate written description and enablement. Appellants respectfully disagree and, therefore, appeal the final rejection of Claims 31 to 33 under 35 U.S.C. §112, first paragraph.

1. The Examiner's Arguments

According to the final rejection, the production of the claimed human TRAF protein requires an isolated nucleic acid for which there is no adequate written description in the specification. The Examiner noted that the "fact that the instant specification discloses a method through which that nucleic acid might or might not be isolated is irrelevant . . . because it is the isolated nucleic acid, not the method of isolating the nucleic acid, which is required to produce and define the claimed protein." (Final Office Action, pages

2-3.) In support of this conclusion, the final Office Action cited *Amgen, Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 USPQ2d, at 1016. Applicants were further encouraged to review the recent CAFC decision in *The Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d 1398. The final rejection additionally referred to the grounds provided in Paper No. 6 for the rejection of original (unamended) claims 31 to 33. According to the latter document, the "instant specification provides no structural or functional information about a human TRAF and no evidence that the murine TRAFs disclosed therein are functionally or structurally predictive of homologous proteins from any other animal." The Examiner noted that the Lewis *et al.* publication (PNAS 88:2830-2834 [1991]), cited by Applicants, states that the amino acid sequences of the human and murine type 1 TNF receptors are only 65% identical, and the amino acid sequences of the human and murine type 2 TNF receptors are only 62% identical. The Examiner added that "since the receptors are not structurally and functionally conserved between mammalian species an artisan would not reasonably expect the proteins associated therewith to be conserved between mice and humans." From this, the Examiner concluded that "the description of a cDNA encoding a TRAF protein and the protein encoded thereby from a mouse does not provide a practitioner of the art with sufficient written description to enable them to make and use a human TRAF protein." The Advisory Action mailed on February 3, 1998 contains the following specific statement: "Product-by-process claims are enabled when that process has been shown to produce the claimed product. No actual product is disclosed in the instant application."

2. Appellants' Arguments

a. The rejection of claims 31 to 33 is improper since the written description and enablement requirements of 35 U.S.C. §112, first paragraph were not separately analyzed.

35 U.S.C. §112 provides in pertinent part that:

"*The specification shall contain a* ***written description*** *of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to* ***enable***

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any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . " (Emphasis added.)

The highlighted terms signal requirements that a patent specification must meet (along with the "best mode" requirement not cited) in order for a patent to be valid. The written description and enablement requirements of §112, first paragraph are separate and distinct from each other (*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116-17 (Fed. Cir. 1991); and MPEP Section 2161), and require different legal and analytical approaches.

The function of the "written description" requirement in §112 is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific invention later claimed by him. Accordingly, the test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed, would reasonably have conveyed to a person of ordinary skill in the pertinent art that the inventor had possession at that time of the later claimed subject matter. *In re Wertheim*, 191 USPQ 90, 96 (CCPA 1976). For this purpose, the description must be sufficiently clear to allow one of ordinary skill to recognize that the applicant invented what is claimed. *In re Lukach*, 169 USPQ 795, 796 (CCPA 1971); *In re Gosteli,* 10 USPQ2d 1614, 1618 (Fed. Cir. 1989); *In re Driscoll,* 195 USPQ 434, 436-438 (CCPA 1977); *In re Wertheim, supra*, at 96-97; *Ralston v. Purina*, 222 USPQ 863, 896 (D.C. D. Kansas, 1984).

In contrast, the purpose of the "enablement" requirement under 35 U.S.C. §112, first paragraph is to ensure that the specification discloses the claimed invention in a manner that enables any person skilled in the pertinent art to make and use the invention. The proper legal approach for an enablement analysis is clearly set forth in the 35 U.S.C. §112, First Paragraph, Enablement Training Manual published by the U.S. Patent and Trademark Office in August 1996. This approach requires that the Examiner starts with a thorough review of the application in its entirety and with a preliminary determination of the scope of the claims. This is followed by a prior art search, and an inquiry whether the specification discloses the claimed invention in a manner that enables a person skilled in the art to make and use the invention without undue

experimentation. *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916); *In re Wands*, 8USPQ2d 1400, 1404 (Fed. Cir. 1988). The determination whether any necessary experimentation is "undue" includes the analysis of the following factors: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples, and (8) the quantity of experimentation needed to use the invention based on the content of the disclosure. *In re Wands, supra.*

The final rejection of Claims 31 to 33 pending in the present application failed to separately analyze these two requirements. An analysis of the factors to be considered in assessing the issue of enablement, including, but not limited to, the above-cited *In re Wands* factors, is entirely missing. The only specific reference to enablement is the following sentence appearing in the Advisory Action maintaining all claim rejections: "Product-by-process claims are enabled when that process has been shown to produce the claimed product." This categorical statement is not supported by any reasoning, case law or other evidence, and, as it will be discussed later, is believed to be clearly erroneous.

Moreover, it appears that, although the written description standard is properly articulated in the paragraph bridging pages 2 and 3 of Paper No. 6, and on page 2 of the final rejection, in the subsequent reasoning, the issue of written description was analyzed under an erroneous standard. This is reflected, for example, in the statement that "the description of a cDNA encoding a TRAF protein and the protein encoded thereby from a mouse does not provide a practitioner of the art with sufficient written description to enable them to make and use a human TRAF protein." (Paper No. 6, emphasis added.) As it is apparent from the foregoing brief review of the pertinent case law, the pertinent query for the issue of written description is not whether a skilled person is enabled to make and use the invention, rather whether a skilled person reading the specification would reasonably conclude that the applicant was in the possession of the invention claimed at the time of the original filing date.

In the absence of a separate and distinct analysis of the written description and enablement requirements of 35 U.S.C. §112, first paragraph, using the proper legal standards, the Examiner failed to

establish a *prima facie* case of unpatentability under this section. Therefore, Applicants respectfully request the reversal of the final rejection of Claims 31 to 33 pending in this application under 35 U.S.C. §112, first paragraph.

b. The specification provides sufficient written description under 35 U.S.C. §112, first paragraph for Claims 31 to 33.

Claims 31 to 33 pending in the present application are product-by-process claims, i.e. claims defining a product in terms of the process by which it is made. The acceptance of such product-by-process claims began more than a century ago, in *Ex parte Painter,* 1891 C.D. (Comm'r of Pats. 1891). Although product-by-process claims were initially granted only when the invention could not be defined otherwise ("the necessity rule"), this rule is no longer applied rigidly. Rather, product-by-process claims are held proper whenever the requirements of §112 are satisfied, provided that other requirements of patentability are also met. *In re Steppan,* 156 USPQ 143 (CCPA 1967); *In re Pilkington*, 162 USPQ 145 (CCPA 1969). The acceptability of product-by-process claims in acknowledged in MPEP §2173.05(p).

In determining compliance with the written description requirement of §112, first paragraph, each case must be decided on its own specific facts, taking into account the nature of the invention and the amount of knowledge imported by the disclosure to those skilled in the art. *In re Driscoll, supra*, at 436-438; *In re Wertheim, supra*, at 96-97; *Ralston v. Purina, supra*, at 896.

In Paper No. 6, the Examiner acknowledged that "[t]he instant specification describes the isolation of cDNAs encoding two TNF receptor associated factor (TRAF) proteins of murine origin and the isolation of the proteins encoded thereby. It also contains ample suggestions that homologous human proteins could be isolated by employing those methods that are routine in the art of molecular biology." However, in the final rejection, the Examiner labelled this teaching "irrelevant", maintaining that, even though the claims are product-by-process claims, under the *Amgen v. Chugai* decision (18 USPQ2d 1016 (CAFC), (hereinafter

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referred to as "*Amgen*") "it is the isolated nucleic acid, not the method of isolating the nucleic acid, which is required to produce and define the claimed protein."

(i) The *Amgen* decision is not directly applicable to the issue of written description with regard to the claims presented and finally rejected in the present application.

In relevant claim under consideration in *Amgen* read as follows:

> "*A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.*" *Amgen*, at 1019.

It was with regard to this claim that the CAFC held that a "*gene is a chemical compound, albeit a complex one*", and its conception does not occur "*unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it.*" *Amgen*, 18 USPQ, at 1021.

Claims 31 to 33 finally rejected in the present application are distinguished from the *Amgen* claim at least in the following aspects:

(1) *Amgen* concerns a product claim, while Claims 31 to 33 of the present application are product-by-process claims.

(2) The product considered in *Amgen* was a purified and isolated DNA, while the product defined in Claims 31 to 33 herein by its mode of preparation is a protein.

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(3) The DNA is the *Amgen* claim is the end product for which patent protection is sought, wherein the DNA in claims 31 to 33 herein is an intermediate for which Applicants do not seek independent patent protection.

(4) The priority dates of the *Amgen* patent (US 4,703,1987) are from 1983/1984, while the present application claims priority to an application filed in 1994.

It is easy to see that *Amgen* does not directly apply to the issue of the sufficiency of written description for Claims 31 to 33 rejected in the present application. Even in absence of the other distinctions, the ten years difference in the relevant dates would warrant a careful separate investigation in view of the fact that the level of the ordinary skill in the art of biotechnology and molecular biology has significantly changed in the last decade.

(ii) Application of the *Amgen* decision by way of analogy does not warrant the conclusion that Claims 31 to 33 lack sufficient written description.

The above-quoted paragraph of *Amgen* specifically allows claims for a product that can be defined "by its mode of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it."

Claims 31 to 33 finally rejected in the present application are product-by-process claims, which define a human TRAF protein by its mode of preparation, and are, therefore, specifically acceptable under *Amgen*. In this regard, the only relevant query is whether the process specified in the claims is sufficiently described in the specification, so as to convey to a person skilled in the art that Applicants were in the possession of the claimed invention at the time of filing their patent application.

It is submitted that such a description is provided in the present application. Human TRAF proteins are specifically included in the definition of "TRAF", and in particular "native TRAF" (page 17, lines 10-14;

page 20, lines 4-8). The nucleotide sequences encoding the murine TRAF1 and TRAF2 proteins, from which the hybridization probes specified in Claims 31 to 33 are prepared, are disclosed at Figure 10 (SEQ ID NO:1) and Figure 11 (SEQ ID NO: 3), respectively. The screening of cDNA libraries with probes derived from TRAF of one species in order to identify nucleic acid encoding a homologous TRAF of another species is described on page 33 and 33 and on page 36, lines 9-19. The passage on page 36, lines 9-19 also discloses the length of oligonucleotide probes, as specified in Claim 31. Stringent hybridization conditions, as recited in Claim 31, are disclosed at page 20, lines 21 to 24. The subsequent steps of inserting the DNA identified into an expression vector, expressing it in a recombinant host cell, and isolating the human TRAF polypeptide produced are amply discussed and exemplified throughout the specification, including, for example, page 29, lines 5-25; page 29, lines 1-10; page 46, line 1 through page 63, line 11; and the examples. The Examiner acknowledged in Paper No. 6 the existence of this disclosure, and that the disclosed techniques are routine. Accordingly, a person skilled in the art of molecular biology, reading this disclosure, had all reason to believe that Applicants considered human TRAF proteins as part of their invention, and were in the possession of a process that was expected to result in the production of such human TRAF proteins with reasonable certainty. The Examiner's suggestion that the fact that the amino acid sequences of the human and murine type 1 TNF receptors are "only" 65% identical, and the amino acid sequences of the human and murine type 2 TNF receptors are "only" 62% identical, and, therefore, only a limited sequence identity would have been expected between the murine and human TRAF proteins associated with the intracellular domains of the TNF receptors, is believed to be irrelevant. Even if one assumes that at the priority date of the present application a person skilled in the art would have expected an about 62-66% identity between the murine and human TRAF proteins, this identity would have been sufficient to successfully identify the human clone by cross-species hybridization with probes designed from a murine TRAF sequence under stringent conditions, as those specified in claim 31.

Indeed, the Lewis et al. reference (PNAS USA 88, 2830-2834 (1991), of record) cited by the Examiner in support of the foregoing conclusion reports

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(1) the isolation of cDNA clones for murine type 1 TNF receptor (mTNF-R1) by screening a murine cDNA library **at low stringency** with a DNA fragment corresponding to the coding region of the human type 1 TNF receptor, and

(2) the isolation of cDNA clones for murine type 2 TNF receptor (mTNF-R2) by screening a murine cDNA library with a 400-bp fragment from the coding region of the human type 2 TNF receptor.

Accordingly, based upon the disclosure provided in the specification, the skilled person would have concluded that human homologues of the murine TRAF1 and TRAF2 proteins could be prepared by screening human cDNA libraries with oligonucleotide probes based on the respective murine sequences, and expression of the DNA obtained in recombinant host cells. In other words, a skilled person reading the disclosure of the present application would have reached the conclusion that, at the priority date of the present application, Applicants were in the possession of the invention claimed in Claims 31 to 33, therefore, the only proper conclusion is that the disclosure present in this application meets the written description requirement of 35 U.S.C. §112, first paragraph.

(iii) The *Lilly* decision is not directly applicable to the issue of written description with regard to the claims presented and finally rejected in the present application.

In *University of California v. Eli Lilly, supra* (hereinafter referred to as the *Lilly* decision) the claim considered by the CAFC read as follows:

> *"A DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin, the plus strand of said cDNA having a defined 5' end, said 5' end being the first deoxynucleotide sequence coding for human proinsulin."*

The following major differences exist between this claim, and Claims 31 to 33 pending and finally rejected in the present application:

(1) *Lilly* concerns a product claim, while Claims 31 to 33 of the present application are product-by-process claims.

(2) The product considered in *Lilly* was a purified a DNA transfer vector, while the product defined in Claims 31 to 33 herein by its mode of preparation is a protein.

(3) The DNA encoding a protein in the *Lilly* claim is the part of the end product for which patent protection is sought, while the DNA in claims 31 to 33 herein is an intermediate for which Applicants do not seek independent patent protection.

It was with regard the above-cited product (vector) claim that the CAFC stated:

"*an adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention.*" *Lilly,* at 1404.

The statement is not directly applicable to a situation where the DNA is not claimed, either in itself or, as in *Lilly*, as part of the product to which the claim is directed.

(iv) Application of the *Lilly* decision by way of analogy does not warrant the conclusion that Claims 31 to 33 lack sufficient written description.

The cited section from *Lilly* follows and relies on the principles set forth in the CAFC's earlier decision in *Fiers v. Sugano*, 25 USPQ 1505 (1993), where the CAFC considered conception of an invention defined in a single count reading as follows:

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"A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide."

Fiers was filed on April 3, 1981 and sought priority of its British application filed on April 3, 1980. Citing *Amgen*, Fiers argued that *Amgen* held that a conception of a DNA can occur in the absence of a disclosure of the sequence of the claimed DNA, provided that an enabling method is disclosed for the preparation of the DNA. Although the CAFC rejected this argument with regard to the above count, it noted that

> *"Our statement in Amgen that conception may occur, inter alia, when one is able to define a chemical by its method of preparation requires that* ***the DNA be claimed by its method of preparation. We recognize that, in addition to being claimable by structure or physical properties, a chemical material can be claimed by means of a process.*** *A product-by-process claim normally is an after-the-fact definition, used after one has obtained a material by a particular process. Before reduction to practice,* ***conception only of a process for making a substance****, without conception of a structural or equivalent definition of that substance,* ***can*** *at most* ***constitute a conception of the substance claimed as a process.*** *Conception of a substance* ***claimed per se*** *without reference to a process requires conception of its structure, name, formula, or definitive chemical or physical properties."*

Fiers, supra, at 1604-1605, emphasis added.

Accordingly, *Fiers*, at least *in dictum*, acknowledges the possibility that the conception of a process for making a substance can constitute a conception of the substance itself claimed as a process, i.e. in a product-by-process format. Nothing in *Lilly* changes this outcome.

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(v) Summary

There is no pertinent case law that would require the disclosure of the nucleotide sequence of a DNA molecule when the invention is a protein (produced by using the DNA molecule as a intermediate) which is defined and claimed in a product-by-process format. On the contrary, in *Fiers* the CAFC expressly allows for the possibility of establishing a valid conception date for a DNA product which is claimed as a product-by-process by relying on the conception date of the process. It follows that similarly, a valid conception date can be established for a protein characterized and claimed in a product-by-process format by reliance on the conception of the (recombinant DNA) process recited in the claim, even if the DNA molecule used in the course of the production of the protein has not been sequenced. This, in turn, means that the disclosure of a sequence for the DNA intermediate is not required for compliance with the written description requirement of 35 U.S.C. §112, first paragraph.

Accordingly, Appellants respectfully request the Board to reverse the final rejection of Claims 31 to 33 under 35 U.S.C. §112, first paragraph for alleged lack of sufficient written description.

c. Claims 31 to 33 are enabled under 35 U.S.C. §112, first paragraph.

There is agreement between Applicants and the Examiner that the process steps recited in Claim 31 are routine, and are sufficiently described in the specification of the current application. The real question is, therefore, whether this is sufficient to provide enablement for the human TRAF protein product claimed in a product-by-process format. In particular, the questions are (i) whether the enablement of the process recited in a product-by-process claim is sufficient to enable the product of that process; and (ii) whether a process including the steps of identifying and expressing a DNA can be enabled without disclosing the nucleotide sequence of the DNA.

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(i) A product-by-process claim is enabled when the process recited for the preparation of the product is enabled.

It is well established that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, the enablement requirement of 35 U.S.C. §112, first paragraph is satisfied. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). This is particularly true when the method for making the claimed invention is recited in the claim. Accordingly, the only possible conclusion in the present case is that if the process for making the human TRAF protein, as recited in finally rejected Claims 31 to 33 is enabled, so is the product of the process, i.e., the human TRAF protein itself.

(ii) The process recited in finally rejected Claims 31 to 33 is enabled without the disclosure of the nucleotide sequence of the DNA used in that process.

(1) *The breadth of the claims*

Claims 31 to 33 are rather narrow. The claims are directed to human homologues of two specific murine TRAF proteins (murine TRAF1 and murine TRAF2), characterized by their process of preparation. Accordingly, even if one assumes that there is more than one human homologue for each murine protein, the number of the human proteins claimed in a product-by-process format is very limited.

(2) *The nature of the invention*

The invention concerns a novel human protein characterized by its production method, which, as the Examiner acknowledged, involves routine steps of recombinant DNA technology.

(3) *The state of the prior art*

The present invention is directed to human proteins associated with TNF receptors. Accordingly, before the present invention, the relevant state of the art concerned type 1 and type 2 TNF receptors, that were known to exist in murine and human species, and were known to show a degree of sequence identity

which allows the identification and isolation of clones encoding the human TNF receptor proteins in a human cDNA library by hybridization, under high stringency conditions, to synthetic oligonucleotide probes based upon the murine sequences.

(4) *The level of one ordinary skill*

It is well established that in the field of recombinant DNA technology the level of skill is quite high, and is usually measured by the skill of a person having obtained a Doctor of Philosophy (Ph.D.) degree in the relevant field.

(5) *The level of predictability in the art*

Although certain areas of recombinant DNA technology are characterized by a relatively high degree of unpredictability, the steps involved in the production of the human TRAF proteins claimed in finally rejected Claims 31 to 33 are not such. As noted before, there is an agreement between the Examiner and Applicants that the claims recite routine steps, i.e. screening a recombinant cDNA library under stringent hybridization conditions, inserting a DNA into an expression vector, transforming a host cell with the expression vector, culturing the transformed host cell, and recovering the human TRAF protein produced. The outcome of these steps is quite predictable. In view of the substantial homology between murine and human TNF receptors, and the fact that (as mentioned before) cDNA clones encoding the murine type 1 and type 2 TNF receptors were identified by screening murine cDNA libraries with sequences from the coding region of the corresponding human proteins, a person skilled in the art would have reasonably viewed the teaching of the present application about the applicability of cross-species hybridization for the identification of the human TRAF proteins as credible, which, coupled with the known steps of recombinant protein expression and purification, would have been expected to yield the human TRAF homologues with reasonable certainty.

The Examiner represented a contrary view stating that

> "The instant specification provides no structural or functional information about a human TRAF and no evidence that the murine TRAFs disclosed therein are

functionally or structurally predictive of homologous proteins from any other animal." Paper 6, page 3.

The Examiner then referred to Lewis *et al., supra*, as allegedly establishing that

"the TNF receptors are not structurally and functionally conserved between mammalian species",

and concluded that, as a result,

"an artisan would not reasonably expect the proteins associated therewith to be conserved between mice and humans."

It is submitted that Lewis *et al.* has been misinterpreted and misapplied. Lewis *et al.* does not teach that the murine and human TNF receptors are not structurally conserved. On the contrary, the authors have found that (1) the extracellular domains of the murine and human TNF receptors are conserved, in particular within the type 1 receptors; (2) intracellular domains of the murine and human TNF receptors are conserved, in particular within the type 2 receptors; (3) murine and human type 1 TNF receptors are similar in that they show similar affinities to murine and human TNF molecules (i.e. are not species specific). (See the Discussion section, and in particular, page 2833, column 2 and page 2834, column 1.) Although the murine type 2 TNF receptor was found to be species specific, this only means, in the authors' interpretation, that species-specific responses are likely to be mediated by the type 2 receptors (both in mice and humans), while the primary mediators of the not species-specific responses are the type 1 receptors (again, both in mice and in the human).

Accordingly, at the priority date of the present application, a person skilled in the art would have viewed the Applicants' teaching of the murine TRAF sequences as reasonably predictive of the existence of respective human TRAF homologues.

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(6) *The amount of direction provided by the inventor*

As noted before, there is ample teaching in the specification for the process claimed in Claims 31 to 33. The nucleotide sequences encoding the murine TRAF1 and TRAF2 proteins, from which the hybridization probes specified in Claims 31 to 33 are prepared, are disclosed at Figure 10 (SEQ ID NO:1) and Figure 11 (SEQ ID NO: 3), respectively. The screening of cDNA libraries with probes derived from TRAF of one species in order to identify nucleic acid encoding a homologous TRAF of another species is described on page 33 and 33 and on page 36, lines 9-19. The passage on page 36, lines 9-19 also discloses the length of oligonucleotide probes, as specified in Claim 31. Stringent hybridization conditions, as recited in Claim 31, are disclosed at page 20, lines 21 to 24. The subsequent steps of inserting the DNA identified into an expression vector, expressing it in a recombinant host cell, and isolating the human TRAF polypeptide produced are amply discussed and exemplified throughout the specification, including, for example, page 29, lines 5-25; page 29, lines 1-10; page 46, line 1 through page 63, line 11; and the examples. The Examiner acknowledged the existence of this disclosure:

> "The instant specification describes the isolation of cDNAs encoding two TNF receptor associated factor (TRAF) proteins of murine origin and the isolation of the proteins encoded thereby. It also contains ample suggestions that homologous human proteins could be isolated by employing those methods that are routine in the art of molecular biology." Paper No. 6, page 3.

As discussed above, the Examiner's reasons for dismissing this teaching in view of the alleged lack of structural conservation and biological differences between the murine and human TNF receptor sequences, is misplaced.

(7) *The existence of working examples*

The specification does not contain working examples for the preparation of human TRAF1 and TRAF2 proteins, however, compliance with the enablement requirement of 35 U.S.C. §112 does not turn on whether an example is disclosed. The specification need not contain an example, if the invention is

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otherwise disclosed in such manner that one skilled in the art will be able to practice it without undue experimentation. *In re Borkowski*, 164 USPQ 642, 645 (CCPA 1970).

Although recent CAFC decisions have established a simultaneous conception and reduction to practice requirement for DNA sequences, such sequences are not claimed in the present application. In all other areas it is still true that an applicant does not need to reduce an invention to practice prior to filing a patent application.

(8) *Quantity of experimentation needed to use the invention based on the content of the disclosure*

There is specific evidence that the disclosure provided in the present application is sufficient to enable the preparation of human TRAF1 and TRAF2 proteins without undue experimentation. Subsequent to the priority date of the present application, Song and Donner, Biochem. J. 809, 825-829 (1995) (of record) disclosed the TRAF2 gene, and Mosialos *et al.*, Cell 80, 389-399 (1995) (of record) disclosed the human TRAF1 gene. The mouse and human TRAF1 proteins are 86% identical on the amino acid level. The amino acid sequence identity between murine and human TRAF2 is 87%. Although the human proteins, similarly to their murine homologues, were identified by using the yeast two-hybrid system, the high degree of sequence identity between murine and human TRAFs clearly permits the isolation of the human clones by hybridization with the coding sequences of the respective murine proteins.

In summary, at the priority date of the present application one reasonably skilled in the art could have practiced the invention claimed in finally rejected Claims 31 to 33 based upon the disclosure provided in the specification and in view of the state of the art, without undue experimentation. Accordingly, the reversal of the rejection of Claims 31 to 33 under 35 U.S.C. §112, first paragraph for alleged lack of enablement is respectfully requested.

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B. THE FINAL REJECTION OF CLAIMS 31 TO 33 UNDER 35 U.S.C. §112, SECOND PARAGRAPH IS IMPROPER AND SHOULD BE WITHDRAWN.

1. The Examiner's Arguments.

In support of the rejection under 35 U.S.C. §112, second paragraph, in the final Office Action, the Examiner noted that the use of the term "about 30 to 50 bases" renders the claim vague and indefinite "because one cannot distinguish between that which is encompassed by this term and that which is excluded. One can not know if an oligonucleotide of 25 bases or 60 bases is or is not encompassed by this term." According to a second ground for rejection under the same section, "the instant specification does not identify that material property of [sic, should be or] combination of properties which is unique to and, therefore, definitive of a TRAF protein for those reasons of record in Paper No. 6." An identically worded rejection in Paper No. 6 was, however, based solely on the use of the term "obtainable" in Claims 31 to 33. As this term is no longer present in amended Claims 31 to 33, which were rejected in the final Office Action, the Examiner has given no reason while the rejection was maintained.

2. Appellants' Arguments.

The use of the term "about" does not render a claim indefinite. In *Ex parte Eastwood*, 163 USPQ 316 (1968) (which was cited in Applicants' response to the final rejection but not addressed by the Examiner), the Patent Office Board of Appeals specifically acknowledged that "the descriptive word 'about' is not indefinite . . . [r]ather the term is clear and flexible and is deemed to be similar in meaning to terms such as 'approximately' or 'nearly'." Indeed, it has been a long standing and consistent practice of the Patent Office to allow this term in claims from a variety of technical fields, including molecular biology. Accordingly, the reversal of the rejection of Claims 31 to 33 on this ground is respectfully requested.

Claims 31 to 33 were further rejected as "vague and indefinite because the instant specification does not identify that material property of [sic] combination or properties which is unique to and, therefore, definitive of a TRAF protein for those reasons of record in Paper Number 6." As noted before, a similar rejection in Paper No. 6 was raised because of the recitation of the term "obtainable" in the rejected claims.

The Examiner interpreted this term as a functional limitation, whereas the claims were being drawn to a composition of matter. The Examiner cited *In re Hutchison*, 69 USPQ 138 (CCPA 1946) to say that "functional statements contained therein do not limit article claims." As the claims, as amended in Applicants' response to Paper No. 6 no longer contain the term "obtainable", it is entirely unclear why this rejection was repeated in the final Office Action. Accordingly, the reversal of the rejection of Claims 31 to 33 for allegedly containing a functional limitation is respectfully requested.

C. CONCLUSION

In conclusion, Appellants again wish to request that the Board overturn the rejection of Claims 31 to 33 under 35 U.S.C. §112, first paragraph. There is no case law that would require the rejection of a claim directed to a novel protein characterized by its process of production for want of adequate written description or enablement, solely because the nucleotide sequence of a DNA molecule used in the course of the production of that protein is not disclosed in the patent application.

Appellants further request that the Board overturn the rejection of Claims 31 to 33 under 35 U.S.C. §112, second paragraph, as clearly erroneous under existing case law.

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In light of the above, Appellants believe that the above arguments warrant reconsideration and withdrawal of the outstanding final rejections herein. Therefore, Appellants respectfully request the Board to revers the final rejection of Claims 31 to 33 and pass this application to issue.

Respectfully submitted,

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Dated: 13 May 1998

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APPENDIX A

31. (Amended) An isolated human tumor necrosis factor receptor associated factor (TRAF) prepared by

(a) screening a human recombinant cDNA library prepared from tissue expressing human TNF-R2 at a detectable level with one or more labeled oligonucleotide probe(s) having about 30 to 50 bases derived from the nucleotide sequence encoding murine TRAF1 (SEQ. ID. NO:1) or murine TRAF2 (SEQ. ID. NO:3) , wherein said probe(s) are designed based on TRAF1 or TRAF2 regions which have the least codon redundance, under stringent conditions comprising overnight incubation at 42° C in a solution comprising 20% formamide, 5xSSC, 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 g/ml denature, sheared salmon sperm DNA;

(b) inserting the DNA hybridizing to said probe(s) into a replicable expression vector;

(c) transforming a recombinant host cell with said expression vector;

(d) culturing the transformed host cell; and

(e) recovering said human TRAF .

32. (Amended) The isolated human TRAF of claim 31, wherein said oligonucleotide probes are derived from the nucleotide sequence encoding murine TRAF1 (SEQ. ID. NO: 1).

33. (Amended) The isolated human TRAF of claim 31, wherein said oligonucleotide probes are derived from the nucleotide sequence encoding murine TRAF2 (SEQ. ID. NO: 3).